RHEUMATIC MANIFESTATIONS OF HIV INFECTION

Internal Medicine Grand Rounds

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But every jet of chaos which threatens to exterminate us is convertible by intellect into wholesome force.

Ralph Waldo Emerson

Autoimmune Phenomena Associated with HIV Infection

Feature	Comment
Polyclonal hypergammaglobulinemia	common
Circulating immune complexes	common
Autoantibodies	
Antinuclear antibody	uncommon, low titer
Rheumatoid factor	uncommon, low titer
Anticardiolipin	common
Antiplatelet	associated with immune thrombocytopenia
AntiRBC	associated with hemolytic anemia
Antigranulocyte	associated with neutropenia
Antilymphocyte	associated with lymphopenia, lymphocyte dysfunction
Miscellaneous plasma findings	
β2 Microglobulin	
Acid-labile interferon	
Soluble IL-2 receptors	

Rheumatic Manifestations of HIV Infection

Arthritis

Reiter's syndrome, reactive arthritis

Psoriatic arthritis

HIV arthritis

Infectious arthritis

Arthralgia Syndromes

Sjogren's Syndrome

Diffuse infiltrative lymphocytosis syndrome

Polymyositis

Vasculitic Syndromes

Rheumatic Manifestations in 101 Persons with HIV Infection

Manifestation	Number	Percentage
Arthralgias	35	34.7
HIV Arthritis	12	11.9
Reiters syndrome	10	9.9
Painful articular syndrome	10	9.9
Psoriatic arthritis	2	1.9
Polymyositis	2	1.9
Vasculitis	1	0.9
None	29	28.9

Reiter's Syndrome

An asymmetric oligoarthropathy in the absence of significant titers of rheumatoid factor or antinuclear antibodies

with one or more of the following:

1. Urethritis or cervicitis

2. Conjunctivitis or uveitis

3. Mucocutaneous involvement
   - circinate balanitis
   - painless oral ulcers
   - keratoderma blennorrhagica

Prevalence of Reiter's Syndrome in Patients with HIV Infection

HIV Positive Patients	Number with Reiter's Syndrome	Prevalence	Location
101	10	9.9	Tampa
90	12	13.3	New York City
47	1	2.0	Cleveland
238	23	9.7	
Non-HIV infected 20-29 year old males		0.06	Minnesota

Presentation of Reiter's Syndrome in Patients with HIV Infection

Cutaneous

- Onychodystrophy
- Psoriaform skin rash
- Keratoderma blennorrhagica

Musculoskeletal

- Enthesopathy/plantar fasciitis
- Dactylitis
- Tenosynovitis
- Oligo or polyarthritis

Other features

- Urethritis
- Diarrhea
- Conjunctivitis

Reactive Arthritis in Patients with HIV Infection

	Features				Onset			
Number of Patients	Urethritis	Conjunctivitis	Keratoderma blennorrhagica	Balanitis	B27+ First	Arthritis First	Simultaneous	HIV First
13	9	10	3	1	9/12	4	4	5
3	3	3	3	3	0/1	0	1	2
2	ND+	ND	ND	ND	2/2	2	0	0
1	1	1	1	1	ND	1	0	0
9	3	2	1	0	3/3	9	0	0
13 *	9	2	ND	4	0/13	ND	ND	ND
10	4	5	1	5	5/8	ND	ND	ND
Total: 51	29/49	23/49	9/36	14/49 19/26δ	19/39	16/28	5/28	7/28

*Zimbabwean patients. Prevalence of HLA-B27 in black Zimbabweans is 0.68

+ No data

δ Excluding Zimbabwean patients

Clinical Features of Reiter's Syndrome in Patients with HIV Infection

* Enthesopathy and fasciitis
* Progression to fibrosis and contractures
* Dactylitis
* Erosive oligo or polyarthritis
* Sacroiliitis without other axial involvement

Features of Reiter's Syndrome
in Patients with HIV Infection

Arthritis - Asymmetric oligo/polyarthropathy
- Course - progressive - 5/13
  remittive - 8/13
- Erosive - 7/13
- Sacroiliac involvement - 10/13
- Enthesopathy - 11/13

Precipitating Infection -
- S. flexneri - 2/13
- C. fetus - 1/13
- Urethritis - 3/13
- Diarrhea - 7/13
- None - 2/13

Cutaneous Involvement - ~ 25%
- Extensive when present

Treatment
- NSAIDs - Modest improvement in joint symptoms
  No effect on skin disease
- AZT - Improves skin disease, not joint symptoms
- Sulfasalazine - Improves joint, bowel symptoms
- Corticosteroids - Effective, ? safety
- Methotrexate, azathioprine - improves all signs and symptoms; induces opportunistic infections

Laboratory Features of Reiter's Syndrome in Patients with HIV Infection

CD4 lymphocyte depletion

CD8 lymphocytes preserved or increased

Marked acute phase response

Hypergammaglobulinemia

No increase in anti-chlamydial antibodies

Reiter's Syndrome in Individuals with HIV Infection

Facts:

Frequency of HLA-B27 : 3 - 9%

Frequency of HLA-B27 in Reiter's syndrome : ~75%

Prevalence of Reiter's syndrome in the population : 0.06%

Prevalence of Reiter's syndrome in HIV infected persons : 2 - 13%

Implication:

Likelihood of developing Reiter's syndrome is greatly increased in HIV infected persons and may involve all HLA-B27 individuals

Evidence for An Immunologic Mechanism in Reiter's Syndrome

* Post infectious onset
* Time interval after infection
* Response to immunosuppressive therapy
* Lymphocytes in lesions
* Susceptibility determined by HLA-B27

Reiter's Syndrome in Persons with HIV Infection

Facts

* Occurs post-infection
* HLA-B27 associated
* More aggressive than that found in HIV-uninfected persons
* CD8+ T cells present or increased
* CD4+ T cells decreased

Implications

* A specific immune recognition event involving HLA-B27 restricted presentation to CD8+ T cells may trigger Reiter's syndrome
* Normally, CD4+ T cells may down regulate this response

Prevalence of Psoriasis and Psoriatic Arthritis in HIV Infected Individuals

Number of Patients	Prevalence		Location
	Psoriasis	Psoriatic Arthritis	
222	1.4	ND [+]	Long Island
50	20.0	10.0	NYC
101	5.0	2.0	Tampa
1000	1.3	ND	Houston
47	ND	2.0	Cleveland
117	0.9	ND	NYC
100	5.0	ND	Dallas
general population	1.6	0.1	

[+] No data

Cutaneous Lesions in 13 Patients with Psoriasis and HIV Infection

Manifestation	Percentage
Seborrheic dermatitis	100
Onychodystrophy	85
Pustular psoriasis (trunk)	15
Psoriasis vulgaris	92
Guttate psoriasis	85
Sebopsoriasis	80
Exfoliative erythroderma	46

Psoriasis in Persons with HIV Infection

1. May develop before or after HIV infection

2. Very aggressive with multiple skin lesions

3. May occur at increased prevalence in HIV infected persons compared to the normal population

4. Overlap with Reiter's syndrome

5. Treatment
   Phototherapy
   AZT
   Etretinate
   Methotrexate - contraindicated

Frequency of Class I MHC Antigens in Psoriasis Vulgaris and Psoriasis in Persons Infected with HIV

Group	B13	B16	B17	B37	B57	CW6
			(percentage)			
Psoriasis vulgaris	15	11	29	7	19	56*
Normal controls	5	5	7	2	7	15
HIV-psoriasis (n=12)	0	9	0	0	0	9
HIV-controls (n=24)	4	4	0	0	4	25
(95% confidence intervals)	0-29	0-37	0-29	0-29	0-29	0-37

HIV Arthritis

Number of patients described : 16

Joints involved : knees, ankles

Duration : 1 - 6 months

Synovial fluid : 50 - 2500 WBC/mm^3

Biopsy : Chronic mild synovitis
Mononuclear cell infiltrate

HLA-B27 : Negative

Rheumatoid factor, ANA : Negative

HIV isolation : 2/16

CONTRASTS BETWEEN REITER'S SYNDROME AND HIV ARTHRITIS

	Reiter's	HIV Arthritis
Pattern of joint involvement		
Monoarticular	+	+
Oligoarticular	+++	+++
Polyarticular	+	+
Synovial fluid WBC	5,000-50,000/mm^3	2,000-5,000/mm^3
Enthesopathies	+++	--
Mucocutaneous lesions, psoriaform rash	+	--
HLA-B27	+(75%)	--

Infectious Arthritis in HIV Infected Individuals

Organism	Joint
Cryptococcus neoformans	Knee
Mycobacterium haemophilum	Wrist
Sporothrix schenckii	MCP, PIP
Histoplasma capsulatum	Knee
Staphylococcus aureus	Acromioclavicular joint

Painful Articular Syndrome

- Severe, debilitating articular pain lasting 2 - 24 hours
- No evidence of synovitis or other signs of inflammation
- Involves knees, shoulders, elbows
- Etiology is unknown
- Treatment : analgesics

Contrasting Features of Idiopathic Sjogren's Syndrome and That Occurring in HIV Infected Individuals

Feature	Sjogren's Syndrome	HIV Infection
Extraglandular	Infrequent Pulmonary, GI Renal, Neurologic	Prominent Pulmonary, GI Neurologic
Infiltrating Lymphocytes	CD4+	CD8+
Autoantibodies	Prominent RF, ANA Anti-Ro/SS-A Anti-La/SS-B	Absent
HLA Association	HLA-B8 HLA-DR2, DR3 HLA-DR4 (RA)	HLA-DR5

The Diffuse Infiltrative Lymphocytosis Syndrome

- HIV infection
- CD8 lymphocytosis
- Diffuse lymphadenopathy
- Diffuse lymphocytic infiltration of salivary glands, lacrimal glands, lung, stomach
- May improve with AZT therapy
- Slow progression to AIDS

Glandular Manifestations of the Diffuse Infiltrative Lymphocytosis Syndrome

Examination	Manifestation	Percentage
Clinical:	Parotid gland enlargement	100
	Xerostomia	80
	Xerophthalmia	50
Radionuclide scan:	Increased uptake in parotid, submandibular, lacrimal glands	100
Histopathology:	Lymphocytic infiltrate	100
Immunohistology:	CD8+ lymphocytes infiltrating gland	100

Extraglandular Manifestations of the Diffuse Infiltrative Lymphocytosis Syndrome

Organ System	Manifestation	Percentage
Lymphatic	Generalized lymphadenopathy	81
Pulmonary	Lymphocytic interstitial pneumonitis	58
Neurologic	VII Nerve palsy	17
	Aseptic meningitis	17
	Motor neuropathy	6
Other	Lymphocytic hepatitis	12
	Gastric lymphocytic infiltrate	6

Diffuse Infiltrative Lymphocytosis Syndrome

Feature	Percentage
ANA: 1:320 or less	12
RF: 1:160 or less	12
Hypergammaglobulinemia	100
WBC > 4,000	100
Lymphocytes > 40%	61
CD8+ lymphocytosis	88

Circulating Lymphocyte Subsets in 16 Patients with the Diffuse Infiltrative Lymphocytosis Syndrome - Absolute CD8 Lymphocytosis and Moderate CD4 Lymphopenia -

Subset	Normal	ARC	AIDS	DILS
		cells/mm^3		
CD8	240-1200	568	662	1820
CD4	390-1770	217	59	371

Outcome in the Diffuse Infiltrative Lymphocytosis Syndrome

Mean follow-up : 33 months

Deceased : 2/17

Pneumococcal pneumonia
Trauma

Opportunistic Infection : 1/17

Cryptococcal meningitis

Diffuse Infiltrative Lymphocytosis Syndrome

Facts:

- An exaggerated CD8 lymphocytic response in HIV infected individuals may lead to glandular and pulmonary infiltration
- This response is limited to HLA-DR5 positive individuals
- This syndrome is associated with a delayed progression to AIDS
- HIV can be cultured from salivary glands

Implication:

An HLA-DR5 restricted (CD4+ T cell) response to an HIV determinant leads to the generation of CD8+ (cytotoxic) T cells that infiltrate organs infected with HIV and suppress viral replication resulting in a clinical picture like Sjogren's syndrome and slow progression to AIDS.

Myopathies Associated with HIV Infection

Polymyositis

Necrotizing, noninflammatory myopathy

Pyomyositis

Infectious myositis with opportunistic organisms

Nemaline (rod) myopathy

Myositis ossificans

AZT-induced myositis

HIV-ASSOCIATED VASCULITIS SYNDROMES

- Polyarteritis (medium-sized vessel disease)
- Leukocytoclastic vasculitis
- Eosinophilic vasculitis
- Isolated vasculitis of the central nervous system
- Lymphomatoid granulomatosis
- Benign lymphocytic vasculitis

Clinical and Laboratory Features of HIV Infection that May Mimic SLE

Constitutional
- fever, malaise, weight loss

Dermatologic
- "butterfly" rash (seborrhea)
- alopecia
- cutaneous vasculitis
- aphthous stomatitis

Musculoskeletal
- arthralgias/arthritis
- myalgia/myositis

Neurologic
- psychosis
- seizures
- peripheral neuropathy

Renal
- azotemia
- proteinuria
- hematuria

Lymphadenopathy

Hematologic
- immune thrombocytopenia
- leukopenia, lymphopenia
- Coombs - positive hemolytic anemia

Immunologic
- antinuclear antibodies
- hypergammaglobulinemia
- circulating immune complexes
- anticardiolipin antibody
- lupus anticoagulant

Rheumatic Conditions that Improve with HIV Infection

1. Rheumatoid arthritis
2. Systemic lupus erythematosus

Implication:

These diseases may be driven by CD4+ T cells. This conclusion is consistent with their association with particular class II MHC determinants, since antigen recognition by CD4+ T cells is restricted by these MHC molecules.

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